AMENDMENTS TO THE SPECIFICATION

Kindly amend the title of the application as follows.

METHOD ~~OF CONSTRUCTING TRANSGENIC~~ FOR PRODUCING GENE TRANSFERRED DENDRITIC ~~CELL~~ CELLS

Kindly insert the following heading and paragraph at page 1, line 4 of the English language specification.

Cross-Reference to Related Applications

This application is the U.S. National Stage of International Application No. PCT/JP2004/016089, filed October 29, 2004, which, in turn, claims the benefit of Japanese Patent Application Nos. 2004-187028, filed June 24, 2004, and 2003-374808, filed November 4, 2003.

Kindly amend the paragraph starting at page 10, line 16 of English language specification as follows.

In addition, the dendritic cells of the present invention include both mature and immature dendritic cells. The immature dendritic cells refer to dendritic cells having low T cell activating ability. Specifically, the immature dendritic cells may have an antigen-presenting ability that is lower than 1/2, preferably lower than 1/4 of that of dendritic cells which maturation had been induced by adding LPS (1 μg/ml) and culturing for two days.

The antigen-presenting ability can be assayed, for example, by allo T cell-activating ability (e.g., a mixed lymphocyte test: allo T cells and dendritic cells are cultured in a mixed culture with a T cell:dendritic cell ratio of 1:10, or preferably with varied ratios; ^{3}H-thymidine is added 8 hours before terminating cultivation, and the T cell growth capacity is assayed based on the amount of ^{3}H-thymidine incorporated into the DNA of the T cells. See Fig. 21; Gene Therapy 2000; 7; 249-254) or by the ability to induce specific cytotoxic T cells (CTLs) using a peptide (e.g., a known class I-restricted peptide of a certain antigen is added to dendritic cells; the dendritic cells are co-cultured with T cells obtained from peripheral blood of the same healthy donor from whom the dendritic cells had been obtained (with 25 U/ml or preferably 100 U/ml of IL-2 on day 3 or later) (preferably stimulated three times during 21 days, more preferably twice during 14 days by dendritic cells); the resulting effector cells are co-cultured with ^{51}Cr-labeled target cells (~~peptide~~ class I-restricted ~~class I~~ peptide positive tumor cells) at a ratio of 20:1, 10:1, 5:1, or 2.5:1, preferably 100:1, 50:1, 25:1, or 12.5:1, for four hours; and ^{51}Cr released from the target cells is quantified. See Fig. 22; Arch Dermatol Res 292:325-332 (2000)). Furthermore, the immature dendritic cells preferably have phagocytic ability for antigens, and more preferably show low (for example, significantly low as compared to mature DCs induced by LPS as described above) or negative expression of receptors that induce the costimulation for T cell activation. On the other hand, the mature dendritic cells refer to dendritic cells that have strong antigen-presenting ability for T cell activation or the

like. Specifically, the mature dendritic cells may have an antigen-presenting ability that is half or stronger, preferably equivalent to or stronger than the antigen-presenting ability of dendritic cells in which maturation has been induced by adding LPS (1 μg/ml) and culturing for two days. Furthermore, the mature dendritic cells preferably have weak or no phagocytic ability for antigen, and more preferably show high expression of receptors that induce the costimulation for T cell activation. The activation of dendritic cells refers to the transition from immature to mature dendritic cell; and the activated dendritic cells encompass mature dendritic cells and dendritic cells in the process of the transition, wherein the expression of CD80 and CD86 that induce costimulatory signals are elevated upon the activating stimuli. In CD11c positive dendritic cells, CD83 positivity serves as an indicator of mature dendritic cells.

Kindly amend the paragraph starting at page 12, line 26 of the English language specification as follows.

CD40 is a type I integral membrane protein of 45 to 48 kD (type I integral membrane glycoprotein). ~~Anti-CD40 antibody~~ CD40 is frequently used as a cell marker (Schlossman, S. *et al.*, eds., 1995, Leucocyte Typing V: White Cell Differentiation Antigens. Oxford University Press, New York; Galy, A.H.M.; and H. Spits, 1992, J. Immunol. 149: 775; Clark, E.A. and J.A. Ledbetter, 1986, Proc. Natl. Acad. Sci. 83:

4494; Itoh, H. *et al.*, 1991, Cell 66: 233; Barclay, N.A. *et al.*, 1993, The Leucocyte Antigen Facts Book., Academic Press).

Kindly amend the paragraph starting at page 17, line 31 of the English language specification as follows.

Herein, a minus-strand RNA virus refers to viruses that include a minus strand (an antisense strand corresponding to a sense strand encoding viral proteins) RNA as the genome. The minus-strand RNA is also referred to as negative strand RNA. The minus-strand RNA virus used in the present invention particularly includes single-stranded minus-strand RNA viruses (also referred to as non-segmented minus-strand RNA viruses). The "single-strand negative strand RNA virus" refers to viruses having a single-stranded negative strand [*i.e.*, a minus strand] RNA as the genome. <u>The minus-strand RNA virus includes</u> ~~Such viruses include~~ viruses belonging to Paramyxoviridae (including the genera *Paramyxovirus*, *Morbillivirus*, *Rubulavirus*, and *Pneumovirus*), Rhabdoviridae (including the genera *Vesiculovirus*, *Lyssavirus*, and *Ephemerovirus*), Filoviridae, Orthomyxoviridae, (including Influenza viruses A, B, and C, and Thogoto-like viruses), Bunyaviridae (including the genera *Bunyavirus*, *Hantavirus*, *Nairovirus*, and *Phlebovirus*), Arenaviridae, and the like.

Kindly amend the paragraph starting at page 33, line 26 of the English language specification as follows.

There is no limitation on the foreign gene to be introduced using the minus-strand RNA virus, and naturally occurring proteins include, for example, hormones, cytokines, growth factors, receptors, intracellular signaling molecules, enzymes, and peptides. The proteins may be secretory proteins, membrane proteins, cytoplasmic proteins, nuclear proteins, and the like. Artificial proteins include, for example, fusion proteins such as chimeric toxin, dominant negative proteins (including soluble receptor molecules or membrane bound dominant negative receptors), truncated cell adhesion molecules, and cell surface molecules. The proteins may also be proteins to which a secretory signal, membrane-localization signal, nuclear translocation signal, or the like has been attached. Functions of a particular gene can be suppressed by introducing and expressing antisense RNA molecule, RNA-cleaving ribozyme, or the like as the transfer gene. When a viral vector is prepared using a gene for treating diseases as the foreign gene, gene therapy can be performed through the introduction of the vector. The viral vector of the present invention is applicable to gene therapy wherein the genes are expressed by direct administration or by *ex vivo* administration, and enables expression of foreign genes for which therapeutic effect can be expected, internal genes short in *in vivo* supply, or the like from dendritic cells. In addition, the ~~method~~ vector of the present invention can also be used as a gene therapy vector in regeneration medicine.

Kindly amend the paragraph starting at page 35, line 36 of the English language specification as follows.

Antigens derived from pathogens include, for example, proteins of hepatitis A virus, hepatitis B virus, hepatitis C virus, hepatitis delta virus, papilloma virus antigen, herpes simplex virus (HSV), varicella-zoster virus (VZV), Epstein-Barr virus, Cytomegalovirus (CMV), HIV, malaria, and the like, or partial peptides thereof. The minus-strand RNA viruses encoding such antigen proteins can be used prophylactically or therapeutically. Specifically, envelopes of influenza highly-virulent strain H5N1 for influenza, envelope proteins of Japanese encephalitis virus (Vaccine, vol. 17, No. 15-16, 1869-1882 (1999)) for Japanese encephalitis, HIV and SIV gag proteins (J. Immunology (2000) vol. 164, 4968-4978), HIV envelope proteins, Nef protein, and other viral proteins for AIDS can be mentioned. In addition, for example, cholera toxin B subunit (CTB) (Arakawa T, *et al.*, Nature Biotechnology (1998) 16(10): 934-8, Arakawa T, *et al.*, Nature Biotechnology (1998) 16(3): 292-7) for cholera; rabies virus glycoprotein (Lodmell DL *et al.*, 1998, Nature Medicine 4(8):949-52) for rabies; and capsid protein L1 of human papilloma virus type 6 (J. Med. Virol, 60, 200-204 (2000)) for cervical carcinoma can be mentioned. Antigen proteins of other pathogenic viruses can also be expressed from the vector. Furthermore, it is possible to use JE-E antigen protein of Japanese encephalitis virus (Japanese Patent Application Kokai Publication No. (JP-A) S64-74982

(unexamined, published Japanese patent application), JP-A H1-285498), gD2 protein of human herpes simplex virus (JP-A H5-252965), polypeptides derived from hepatitis C virus (JP-A H5-192160), polypeptides derived from pseudorabies virus (Japanese Patent Kohyo Publication No. (JP-A) H7-502173 (unexamined Japanese national phase publication corresponding to a non-Japanese international publication), and the like. For example, cells derived from patients infected with such pathogenic microorganisms may be analyzed to identify an epitope of an antigen protein to be presented on antigen-presenting cells (APC) for use. It is preferred to appropriately select the HLA type and identify an epitope corresponding to the desired HLA for use.